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Association of Parental Substance Use Disorder with Offspring Cognition: A Population Family-based Study

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Abstract

Aims

To assess whether parental substance use disorder (SUD) is associated with lower cognitive ability in offspring, and whether the association is independent of shared genetic factors.

Design

A population family-based cohort study utilizing national Swedish registries. Linear regression with increased adjustment of covariates was performed in the full population. In addition, the mechanism of the association was investigated with children-of-sibling analyses using fixed-effects regression with three types of sibling-parents with increasing genetic relatedness (half-siblings, full siblings and monozygotic twins).

Setting and participants

A total of 3,004,401 people born in Sweden between 1951 and 1998.

Measurements

The exposure variable was parental SUD, operationalized as having a parent with lifetime SUD diagnosis or substance related criminal conviction in the National Patient Register or Crime Register, respectively. Outcomes were cognitive test score at military conscription and final high school grades. Covariates included in the analyses were sex, birth year, parental education, parental migration status and parental psychiatric co-morbid diagnoses.

Findings

In the full population, parental SUD was associated with decreased cognitive test stanine scores at conscription (4.56 [4.55 - 4.57]) and lower z-standardized high school grades (-0.43 [-0.43 - -0.42]) compared to people with no parental SUD (Cognitive test: 5.17 [5.17 - 5.18]; Grades: 0.09 [0.08 - 0.09]). There was evidence of a dose-response relationship, in that having two parents with SUD (Cognitive test: 4.17 [4.15 - 4.20]; Grades: -0.83 [-0.84 - -0.82]) was associated with even lower cognitive ability than having one parent with SUD

(Cognitive test: 4.60 [4.59 - 4.60]; Grades: -0.38 [-0.39 - -0.38]). In the children-of-siblings analyses when accounting for genetic relatedness, these negative associations were attenuated, suggestive of shared underlying genetic factors.

Conclusions

There appear to be shared genetic factors between parental substance use disorder (SUD) and offspring cognitive function, suggesting that cognitive deficits may constitute a genetically transmitted risk factor in SUD.

Introduction

Substance use disorders (SUD) constitute a global public health problem contributing to substantial morbidity and mortality worldwide (1). SUD run in families and have a heritability, i.e., proportion of variance explained by genetic factors, of 30-70% based on twin and family studies (2). There is a large body of research reporting negative associations between parental SUD and cognition in offspring, manifested as lower academic achievement (3–6) and lower general intelligence (7–10). Furthermore, healthy individuals with positive family history of SUD, compared to individuals without family history, exhibit specific cognitive deficits, e.g. in different domains of executive function (11,12). To what degree these impairments in cognitive function are caused by environmental (e.g., unstructured home environment, nutrition, lack of cognitive stimuli) or genetic factors associated with having a parent with SUD, is currently not known.

Cognitive ability is one of the most well studied phenotypes in quantitative behavioural genetics, and repeated studies using different assessment methods have shown heritability estimates being typically 50% or higher (13). Patients suffering from SUD across all substances of abuse exhibit a wide range of cognitive deficits (14–17), which contributes to progression of the disease and affects attrition to treatment. Even though substance intake in itself causes acute cognitive deficits (18–22), reduced cognitive ability in adolescence and young adulthood is also known to predict the development of SUD (23–27), and this association is partly explained by shared genetic factors (23,28). Taken together, previous research suggests that the cognitive deficits observed in SUD are partly pre-morbid, and may index the genetic risk for developing SUD. To the best of our knowledge, however, no previous study has investigated the association between parental SUD and cognitive ability in offspring using large-scale population-based datasets with information about genetic relatedness.

The aims of the current study were twofold. First, we investigated the association of parental SUD with offspring cognitive ability in young adults and adolescents operationalized as cognitive test score at the mandatory military conscription and school grades, respectively. Second, by utilizing a family-based study design accounting for genetic relatedness, we investigated whether this association was independent of shared genetic factors.

Methods and Materials

Study population

We conducted two population-based cohort studies utilizing several Swedish national registries. All Swedish citizens have a unique personal identity number which enables deterministic linkage between the different registries (29). The study included two separate but partly overlapping cohorts. Cohort 1 included all men born in Sweden 1951-1992 with available cognitive testing data from conscription (N=1,215,690). Since mandatory military conscription in Sweden ended 2010, individuals who were born 1992 were thus the last birth cohort who underwent cognitive testing at conscription. Cohort 2 included all individuals (i.e.

both boys and girls) born in Sweden 1971 – 1998 with school grades (N=2,517,030). We analyzed the two cohorts/cognitive outcomes separately, i.e., an individual could be included in both cohorts, but all individuals were unique within each cohort study. See Supplementary Information (SI) for further details of cohort definition and national registries.

Exposure

The exposure of interest was parental SUD, defined as having a parent with either any alcohol or drug abuse/dependence International Classification of Disease (ICD) diagnosis in the National Patient Register which has nationwide coverage of inpatient/outpatient diagnoses since 1973/2001 (ICD 8:291, 303 and 304; ICD 9:291, 292, 303, 304, 305A, 305X; ICD 10:F10-F19, except F17). See Table S1 in SI for complete description of the included SUD related diagnoses. Given the high prevalence of SUD in drug related criminal offenders (30), SUD was also defined by having a criminal conviction of any substance related crime (e.g. drunk driving) extracted from the Crime Register which includes court convictions since 1973.

Outcomes

In cohort 1, cognitive function was assessed at military conscription using the Swedish Enlistment Battery (SEB) which measures general cognitive ability reported as a standardized stanine score (nine-point scale with a mean of 5 and a standard deviation of 2). The SEB consists of several subtests (See SI for further details), has good psychometric properties (31,32) and has been used in several previous epidemiological studies (26,33) In cohort 2, cognitive function was operationalized as final school grades when graduating from compulsory education at age 15-16. There were two different grade systems during 1988-1997 and 1998-2013 ranging between 0 – 5 and 0 – 320, respectively. Data were extracted from the National School Register, z-standardized and collapsed into one variable covering both time periods.

Statistical Analysis

The following analytical procedure was performed for both study cohorts: First, the association between parental SUD and offspring cognition was analysed using linear regression, with a cluster-robust sandwich estimator allowing for adjustment of standard errors due to the dependence of offspring siblings. To control for age, time period and sex effects, model 1 adjusted for birth year in both offspring and parents and sex. Given the association between socioeconomic status (34) and psychiatric disorders (35) on cognitive function, model 2 adjusts for the potential confounding factors parental education, parental psychiatric disorders (except SUD), parental immigration status and the co-parent's SUD status. The final model 3 adjusts for an additional risk factor namely early onset of psychiatric disorder in offspring, since a majority of psychiatric disorders are associated with cognitive deficits (35). See SI for detailed definitions of all covariates.

Second, children-of-siblings analyses were performed by fitting conditional linear regression models (i.e. fixed-effects regression models) (36,37) within offspring to pairs of brothers and sisters in the parent generation. By design, the fixed-effects model rules out all factors which are shared between members of the clusters (i.e., extended families). As a results, this family-based design allows for gradually increasing adjustment of genetic confounding by including offspring of siblings with different degree of genetic relatedness whose parents are discordant for SUD (38,39). Three separate models for offspring with the following relationships between the sibling parents were fitted: Half-sibling parents (who share on average 25% of their co-segregating alleles); Full sibling and dizygotic twin parents (who share on average

50% of their co-segregating alleles) and monozygotic (MZ) twin parents (who share 100% of their co-segregating alleles). If the association remained similar across different degrees of genetic relatedness amongst the parents, this would suggest that the association was not due to genetic confounding factors. In contrast, if the associations were reduced or even disappeared with increasing genetic similarity between parents, this would indicate that shared genetic factors contributed to the associations found in the full population regression analyses. For each sibling parent type, three models were fitted with increasing adjustment for covariates as described above for the linear regression models. Two siblings in the parent generation and one offspring per nuclear family were randomly selected, and the analyses were conducted separately for sibling fathers and mothers.

Several sensitivity analyses were also performed. First, for a more detailed view on different parental substance misuse behaviours, we conducted the population-level analyses separately for parental alcohol use disorder (AUD), drug use disorder (DUD), and substance related criminality (SRC). Second, we employed a more restricted definition of parental SUD, excluding intoxication diagnoses (F1X.0 in ICD-10) and repeated the main analysis. Third, in cohort 2 we investigated a potential gender difference by repeating the main analysis separately for boys and girls. Fourth, in a subsample with parental cognitive testing or grade data available, we repeated the population-level analyses including parent cognitive test score or grades as a covariate in all models. Fifth, the population-level analysis was repeated in offspring whose parents were at least 15 years old in 1973 at the start of register coverage of psychiatric diagnoses and criminal convictions. Sixth, to investigate influence of ethnic diversity, the population-level analysis was repeated in offspring who had at least one parent not born in Sweden. Seventh, to investigate influence of early SUD, we repeated the main analysis with parental SUD operationalized as having a first SUD event prior to birth of offspring. Finally, to further adjust for potentially confounding socioeconomic factors, we repeated the population analysis while further adjusting for parental income, divorce status and geographic region (See SI for complete description of covariates).

Results

Our total cohort included 3,004,401 unique individuals, of which 418,831 had a father with SUD and 129,374 had a mother with SUD. The total number of fathers and mothers with SUD was 219,581 and 68,500, respectively. In the fathers with SUD, the rate of AUD, DUD and SRC were 45%, 12% and 77%, respectively. The corresponding rates for mothers with SUD were 60% (AUD), 32% (DUD) and 40% (SRC). A complete description of the parents with SUD, including different forms of substance type diagnoses (e.g., opioids, cocaine), is presented in the SI (Table S2). As shown in Table 1 of all unique individuals, offspring with parental SUD had lower cognitive test score and lower grades compared to those without parental SUD. The estimates were similar for maternal SUD and paternal SUD, while having two parents with SUD was associated with even lower cognitive score compared to having one parent with SUD. Parents with SUD also had lower education, higher prevalence of psychiatric co-morbidity, and were more likely to be immigrants (Table 1).

Results from the regression analyses of parental SUD predicting cognitive test score and school grades are presented in Table 2. In model 1, adjusting for offspring sex and birth year in parents and offspring, parental SUD predicted a change of -0.54 [95 % confidence interval: -0.55; -0.53] stanine units and -0.48 [-0.48; -0.47] standard deviations in offspring cognitive test score and school grades, respectively. When adjusting for parental education, psychiatric co-morbidity, immigration status (model 2) and offspring psychiatric co-morbidity and SUD before conscription/graduation year (model 3), the estimates were reduced by approximately 40-50%.

The children-of-siblings analyses found that the associations between parental SUD and offspring cognitive function were attenuated in models increasingly accounting for genetic factors. Tables 3 and 4 report the results of the children-of-siblings analyses for high school grades and cognitive test scores, respectively. For instance, the regression coefficient for maternal SUD and school grades (Table 3A) was gradually reduced from -0.55 [-0.56; -0.54] in the population to -0.35 [-0.40; -0.31] in children-of-half-siblings, -0.31 [-0.33; -0.28] in children-of-full-siblings, and -0.16 [-0.52; 0.21] in children-of-MZ-twins. The overall pattern was similar across both paternal and maternal SUD, except for the association between maternal SUD and cognitive test scores where the estimate for offspring of MZ twins was similar to the population estimate (Population: -0.54 [-0.56; -0.52]; Children-of-MZ-twins: -0.95 [-1.76; -0.13]. The overall pattern of gradual reductions of associations with increasing genetic relatedness in parents also remained with increasing adjustment of measured parental (model 2) and offspring (model 3) covariates.

The first sensitivity analysis found that population regression estimates for different forms of SUD were in the same range as the main results (Tables S3-S5). Secondly, when employing a more conservative definition of parental SUD (excluding all intoxication diagnoses), the results were similar as in the main analysis (Tables S6-S8). Third, when analyzing boys' and girls' high school grades separately, we did not find any indication of significant sex difference in the association of parental SUD with grades, given very similar regression coefficients in the full population (Table S9), and completely overlapping 95% CIs between boys and girls for both maternal and paternal SUD in the within-family models (Tables S10 A-C and S.10 B-D). Fourth, the associations attenuated but had a similar pattern even after adjusting the models for parental cognitive outcomes (Table S11), when only including parents with a complete coverage in the registries (Table S12), who were immigrants (Table S13), and who had the first SUD event prior to the birth of offspring (Table S14). Finally, the results remained unchanged when adjusting for additional socioeconomic covariates including parental income, divorce status and geographic region (Table S15-16). A summary of the sensitivity analyses at the population level using different exposure definitions of parental SUD is presented in Table S17.

Discussion

In a large-scale population based study of 3 million individuals using Swedish national registries, we found a robust negative association between parental SUD and cognitive function in offspring. There was evidence of a dose-response relationship, in that having two parents with SUD was associated with even lower cognitive ability than having one parent with SUD. The current study is the largest study to date investigating this research question. Furthermore, the population regression results were similar in both cohorts using two different outcome measures of general cognitive ability, suggesting that the association is robust, and not dependent on any specific test or administration procedure. Finally, given the unique possibility to link different population registries, the current study could exert a stringent adjustment of different parental and offspring covariates.

To the best of our knowledge, no previous study has investigated the mechanism of the association between parental SUD and cognitive function in offspring using a family-based design. The negative association between parental SUD and offspring cognition found in the population, was gradually reduced and finally disappeared with increased adjustment for genetic confounding factors. Our results are in line with previous studies indicating a genetic overlap between cognitive ability and SUD within individuals (23,40,41), and extend these findings to an intergenerational association between parental SUD and offspring cognition. The negative associations found at the population level were generally reduced by 40-60% in the analyses of offspring to full siblings discordant for SUD. Furthermore, for offspring to monozygotic twins discordant for SUD, the coefficient estimates in general approached zero and were not statistically significant, suggesting that genetic confounding substantially explained the association.

The results also suggest a possible parental sex difference in the association of offspring cognition with parental SUD. For cognitive ability measured at conscription in male offspring, the negative association of maternal SUD with offspring cognitive function remained statistically significant also when adjusting for genetic factors. In the sensitivity analyses of grades however, the corresponding estimates in the maternal SUD children-of-MZ-twins analysis were not significantly different from zero. One possible interpretation is that maternal SUD actually has a negative effect on cognitive ability in the offspring possibly mediated by a different mechanism than paternal SUD. Potential mechanisms underlying the effect could include intrauterine toxic effects of substance intake during pregnancy, which is known to severely affect cognition in fetal alcohol spectrum disorder (42). Another possibility could be different parenting behaviour by fathers and mothers which, when afflicted by SUD, may be differentially reflected in the offspring's cognitive development (43). However, it is important to note that given the lower frequency of MZ twins and maternal SUD in the population, the maternal SUD children-of-siblings analyses had lower statistical power yielding more unreliable estimates. Further studies are thus needed to confirm this tentative finding.

Our findings of shared genetic factors between parental SUD and offspring cognition are compatible with a large body of previous research showing that lower cognitive function predicts the development of SUD (23–27). Compared to healthy controls, individuals suffering from SUD exhibit a wide array of cognitive deficits (14–16). Our results further add an important dimension to this body of literature by demonstrating that the associations found in previous studies to a substantial degree can be explained by genetic factors and not caused only by toxic effects of substance intake. A recent meta-analysis (14) on cognitive deficits in alcohol use disorder found that the effect sizes for differences between patients and healthy controls observed in early abstinence (Cohen's d = 0.33 – 0.70) were reduced but still remained statistically significant after long-term abstinence (Cohen's d = 0.13 – 0.30). Interestingly, we found similar effect sizes for the effect of parental SUD on the cognitive outcomes used in the current study (Cohen's d = 0.30 – 0.40). Thus, we conclude that family history of SUD might explain a substantial part of the previously observed cognitive deficits in the patient population, highlighting the importance of assessing SUD family history when evaluating cognitive impairments in research, as well as clinical practice. Furthermore, our sensitivity analyses found similar negative associations across all different forms of parental SUD, including AUD, DUD and SRC, suggesting lack of substance-specific effects. Behavioural genetic analyses have supported the view of SUD as part of a wider externalizing spectrum of disorders (44), it is likely that our findings of shared genetic factors may also be shared with other externalizing disorders sharing genetic factors with SUD such as ADHD (45).

Earlier studies have found that offspring of SUD parents exhibit a wide array of specific cognitive impairments, such as elevated impulsivity (46), poor planning ability (46), impaired attention (46–48), reduced visuospatial capacity (48), impaired set shifting (49) and lower verbal ability (7). Whether these associations are explained by parental SUD being genetically associated with general cognitive ability or specific cognitive deficits remains an open research question. Ersche and colleagues studied patients with central stimulant use disorder, their healthy siblings and healthy individuals and found that patients and their healthy siblings had elevated impulsivity (50), impaired executive function (12) and reduced response inhibition with associated fronto-striatal brain abnormalities (51) implying a common underlying neurocognitive phenotype. Clinical and genetically informed studies ofdifferent SUD populations are needed to further characterize the cognitive profiles transmitted across generations in families with SUD.

There are important methodological considerations of relevance for the current study. First, it is possible that other factors than genuine cognitive ability could affect the cognition outcomes. For instance, subjects with low motivation may have purposefully performed worse at cognitive testing in order to evade military service. Similarly, it is possible that environmental factors related to different high schools could affect the levels of grades. However, the fact that the two different measures of cognitive ability, collected in different circumstances, still yielded similar results supports the overall conclusions of the study. There was also an evident association between the two cognitive outcomes (correlation=0.604, $p<0.0001$) supporting that these variables at least in part capture general cognitive ability. Second, there is always a risk of misclassification when utilizing registry-based data, and this could bias the results to mimic the pattern of genetic confounding (52). For instance, not all parents with SUD will be detected in the registries and since the registries started recording psychiatric diagnoses from 1973 the oldest parents were not covered by the registries for a large portion of their lives. We tried however to reduce this risk by including both medical and criminal register data for a broader definition of SUD.

Furthermore, in a sensitivity analysis we found similar regression coefficient estimates for the subsample of offspring (n=185,713) whose parents were more fully covered in the registries. Third, there is a possibility that individuals with SUD with lower cognitive ability are more likely to be captured by the registries. However, in a sensitivity analysis adjusting for parental cognition the overall pattern of associations were similar as in the main analysis. This suggests that differential detection of SUD in parents with lower cognition did not fully explain our findings. Fourth, it is possible that our findings do not transfer to other populations and socio-cultural settings. However, several hundred thousands of individuals in our cohort did have parents with immigrant background, allowing us to do a sensitivity analysis only including these specific individuals. In this analysis we found that the overall negative association of parental SUD was similar as in the full population, suggesting parental immigrant status did not affect the overall conclusion of the study. Future studies in other sociocultural settings and populations with different genetic constitutions are needed to investigate the generalizability of our findings. Finally, it is important to consider that family-based study designs are based on several important assumptions (53), e.g., that the results generalize to families without cousins.

Our findings have general implications for educational and mental health services. First, children with parental SUD may, in addition to other forms of social and emotional support, also benefit from targeted educational support to alleviate the negative impact of lower cognitive ability. Second, treatment and psychoeducation programs for SUD should take into consideration that cognitive deficits observed in SUD may not completely resolve despite abstinence, since the cognitive deficits could in part be a manifestation of elevated genetic risk for SUD. For instance, targeting cognitive deficits through cognitive training has been proposed as a novel treatment strategy in SUD (54) with limited or no effect in clinical populations so far (55,56). The results of the current study highlight the importance for treatment studies to also assess SUD family history since this may be an important moderating factor for treatment response, specifically when investigating cognitive test outcomes. Third, our results have possible implications for future diagnostic criteria of SUD, which at present in the DSM-5 do not explicitly refer to cognitive deficits (57). If genetically influenced cognitive deficits indeed are inherent to the SUD syndrome, as our study suggests, assessment of cognitive function could constitute possible future diagnostic criteria (similar to difficulties of concentration in major depression) or as a specifier of diagnosis (similar to ADHD inattentive or hyperactive form) in SUD. Furthermore, knowledge of those specific cognitive phenotypes could also improve early prevention of SUD, by improving methods of early identification of high-risk individuals. Our findings could thus potentially have important implications for both diagnostic classification and prevention of SUD.

In summary, our results show that parental SUD robustly predict poorer cognitive function in offspring. Furthermore, we found that this association to be dependent on shared genetic factors, suggesting that cognitive phenotypes in part index genetic risk for SUD.

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Table 1. Cognitive test score at conscription, high school grades and parental background characteristics in 3,004,401 individuals born in Sweden 1951 – 1998. Values in brackets are 95% confidence intervals.

	Substance use disorder in parents					
	None (n=2,503,699)	SUD in any parent (n=500,702)	SUD in father (n=418,831)	SUD in mother (n=129,374)	SUD in one parent (n=453,199)	SUD in two parents (n=47,503)
Cognitive test score[a]	5.17 [5.17 ; 5.18]	4.56 [4.55 ; 4.57]	4.54 [4.53 ; 4.55]	4.49 [4.47 ; 4.50]	4.60 [4.59 ; 4.60]	4.17 [4.15 ; 4.20]
Grades[b]	0.09 [0.08 ; 0.09]	-0.43 [-0.43 ; -0.42]	-0.43 [-0.44 ; -0.43]	-0.56 [-0.57 ; -0.55]	-0.38 [-0.39 ; -0.38]	-0.83 [-0.84 ; -0.82]
Fathers education[c]	3.54 [3.54 ; 3.54]	3.03 [3.03 ; 3.04]	2.98 [2.98 ; 2.99]	3.09 [3.09 ; 3.10]	3.06 [3.05 ; 3.06]	2.78 [2.77 ; 2.79]
Mothers education[c]	3.79 [3.79 ; 3.79]	3.37 [3.37 ; 3.38]	3.39 [3.38 ; 3.39]	3.19 [3.18 ; 3.19]	3.41 [3.41 ; 3.42]	2.99 [2.97 ; 3.0]
Fathers psychiatric disorder (%)	7.83 [7.79 ; 7.86]	25.77 [25.65 ; 25.90]	28.75 [28.61 ; 28.88]	18.90 [18.68 ; 19.11]	25.0 [24.87 ; 25.12]	33.25 [32.83 ; 33.68]
Mothers psychiatric disorder (%)	11.76 [11.72 ; 11.80]	27.45 [27.33 ; 27.58]	21.38 [21.26 ; 21.51]	58.27 [58.0 ; 58.54]	24.27 [24.14 ; 24.39]	57.84 [57.40 ; 58.29]
Father immigrant (%)	10.65 [10.62 ; 10.69]	14.32 [14.23 ; 14.42]	14.62 [14.52 ; 14.73]	13.42 [13.24 ; 13.61]	14.30 [14.20 ; 14.41]	14.52 [14.20 ; 14.84]
Mother immigrant (%)	10.18 [10.14 ; 10.22]	12.63 [12.53 ; 12.72]	12.81 [12.71 ; 12.91]	12.07 [11.89 ; 12.24]	12.61 [12.52 ; 12.71]	12.73 [12.43 ; 13.03]

[a] Sample size for cohort with cognitive test score at conscription was N=1,215,690

[b] Sample size for cohort with final high school grades was N=2,517,030

[c] Education category (range 1-7) is reported as mean, but in the statistical analysis it was treated as a categorical variable.

Table 2. Population regression analyses: Parental substance use disorder (SUD) as a predictor of cognitive test score at conscription (A) and high school grades (B). Values presented are unstandardized regression coefficients and 95% confidence intervals in brackets. Standard errors were adjusted for the clustering of siblings.

A. Cognitive test score			
Full sample (n)	SUD in any parent	SUD in one parent	SUD in two parents
Model 1[a] (n=1,215,690)	-0.54 [-0.55 ; -0.53]	-0.51 [-0.52 ; -0.50]	-0.89 [-0.92 ; -0.86]
Model 2[b] (n= 1,202,017)	-0.32 [-0.33 ; -0.32]	-0.31 [-0.32 ; -0.30]	-0.49 [-0.53 ; -0.46]
Model 3[c] (n=1,202,017)	-0.31 [-0.32 ; -0.30]	-0.30 [-0.31 ; -0.29]	-0.47 [-0.50 ; -0.44]
B. Grades			
Full sample (n)	SUD in any parent	SUD in one parent	SUD in two parents
Model 1[a] (n=2,517,030)	-0.48 [-0.48 ; -0.47]	-0.44 [-0.44 ; -0.43]	-0.86 [-0.87 ; -0.85]
Model 2[b] (n= 2,499,592)	-0.30 [-0.31 ; -0.30]	-0.28 [-0.28 ; -0.28]	-0.54 [-0.55 ; -0.52]
Model 3[c] (n=2,499,592)	-0.30 [-0.30 ; -0.29]	-0.27 [-0.28 ; -0.27]	-0.52 [-0.53 ; -0.51]

[a] Model 1 adjusted for birth year in offspring and parents (and sex in the grade analysis).

[b] Model 2 further adjusted for parental education, any parental psychiatric disorder (except SUD), parental immigration status and the other parent's SUD status.

[c] Model 3 further adjusted for any psychiatric disorder or SUD in offspring before conscription/graduation.

Table 3. Children-of-siblings analysis: Maternal (A) and paternal (B) substance use disorder (SUD) as a predictor of offspring's final high school grade in the full population (linear regression) and the within-family-models with increasing genetic similarity in offspring (fixed-effects regression).

A. Maternal SUD		Within-Family-models		
	Full population N=2,517,030	Children of half siblings N=60,816	Children of full siblings N=387,988	Children of MZ-twins N=2,736
Model 1[a]	-0.55 [-0.56 ; -0.54]	-0.35 [-0.40 ; -0.31]	-0.31 [-0.33 ; -0.28]	-0.16 [-0.52 ; 0.21]
Model 2[b]	-0.27 [-0.27 ; -0.26]	-0.17 [-0.22 ; -0.13]	-0.19 [-0.21 ; -0.16]	-0.11 [-0.49 ; 0.27]
Model 3[c]	-0.26 [-0.27 ; -0.25]	-0.17 [-0.21 ; -0.12]	-0.18 [-0.20 ; -0.16]	-0.14 [-0.51 ; 0.24]
B. Paternal SUD		Within-Family Models		
	Full population N=2,517,030	Children of half siblings N= 52,670	Children of full siblings N= 384,604	Children of MZ-twins N= 1,956
Model 1[a]	-0.47 [-0.47 ; -0.46]	-0.36 [-0.39 ; -0.33]	-0.27 [-0.28 ; -0.25]	-0.06 [-0.28 ; 0.16]
Model 2[b]	-0.28 [-0.28 ; -0.28]	-0.23 [-0.26 ; -0.20]	-0.19 [-0.21 ; -0.18]	0.02 [-0.19 ; 0.23]
Model 3[c]	-0.27 [-0.28 ; -0.27]	-0.22 [-0.25 ; -0.19]	-0.19 [-0.20 ; -0.17]	0.02 [-0.19 ; 0.24]

[a] Model 1 adjusted for birth year in offspring and parents (and sex in the grade analysis).

[b] Model 2 further adjusted for parental education, any parental psychiatric disorder (except SUD), parental immigration status and the other parent's SUD status.

[c] Model 3 further adjusted for any psychiatric disorder or SUD in offspring before conscription/graduation.

Table 4. Children-of-siblings analysis: Maternal (A) and paternal (B) substance use disorder (SUD) as a predictor of offspring's cognitive test score at conscription in the full population (linear regression) and the within-family-models with increasing genetic similarity in offspring (fixed-effects regression).

A. Maternal SUD		Within-Family-models		
	Full population N=1,215,690	Sons of half siblings N=24,354	Sons of full siblings N=219,524	Sons of MZ-twins N=1,448
Model 1[a]	-0.54 [-0.56 ; -0.52]	-0.28 [-0.40 ; -0.15]	-0.21 [-0.27 ; -0.15]	-0.95 [-1.76 ; -0.13]
Model 2[b]	-0.25 [-0.27 ; -0.23]	-0.13 [-0.27 ; -0.00]	-0.09 [-0.15 ; -0.03]	-0.97 [-1.77 ; -0.17]
Model 3[c]	-0.23 [-0.25 ; -0.21]	-0.12 [-0.26 ; 0.01]	-0.08 [-0.14 ; -0.02]	-0.94 [-1.77 ; -0.12]
B. Paternal SUD		Within-Family Models		
	Full population N=1,215,690	Sons of half siblings N= 19,122	Sons of full siblings N= 209,338	Sons of MZ-twins N=1,084
Model 1[a]	-0.54 [-0.55 ; -0.53]	-0.46 [-0.55 ; -0.36]	-0.28 [-0.31 ; -0.24]	0.23 [-0.29 ; 0.75]
Model 2[b]	-0.31 [-0.32 ; -0.30]	-0.32 [-0.41 ; -0.22]	-0.19 [-0.23 ; -0.16]	0.29 [-0.21 ; 0.79]
Model 3[c]	-0.30 [-0.31 ; -0.29]	-0.31 [-0.40 ; -0.21]	-0.19 [-0.22 ; -0.15]	0.29 [-0.21 ; 0.80]

[a] Model 1 adjusted for birth year in offspring and parents (and sex in the grade analysis).

[b] Model 2 further adjusted for parental education, any parental psychiatric disorder (except SUD), parental immigration status and the other parent's SUD status.

[c] Model 3 further adjusted for any psychiatric disorder or SUD in offspring before conscription/graduation.